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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group	335	*(Our Case)*	3220-18158
Applicant:	Richard B. Borgens et al.		
Invention:	METHOD AND APPARATUS FOR REGENERATING NERVES		
Serial No:	258,142		
Filed:	October 14, 1988		
Examiner:	G. Manuel		

Certificate Under 37 CFR 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231

on October 20, 1989

Roland A. Fuller III
Attorney 31160

Dated: 10/20/89

DISCLOSURE STATEMENT

Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

Applicants make of record the documents listed on the attached form PTO-1449. Copies are enclosed.

C. D. McCaig, "Spinal Neurite Reabsorption and Regrowth in vitro Depend on the Polarity of an Applied Electric Field," Development, 100, 31-41 (1987), discloses that in embryonic spinal neurities of frogs, the application of a steady state DC electrical field would stimulate neurite growth toward the cathode almost immediately and that reabsorption of anodally facing neurites would begin only after a period of time elapsed. Further, McCaig discloses that the rate of reabsorption of anodally facing neurites begins slowly and increases over time. The maximal phase of reabsorption of anodal facing neurities was disclosed as taking place during a twenty minute period about one hour after the onset of reabsorption. McCaig also discloses that when the polarity of the electrical field is reversed, reabsorption of the initially anodal facing neurites halts and growth of the neurite in that

direction is now stimulated. McCaig then postulated that if his results reflected what might happen in vivo, then an optimal regime for electrical stimulation across a lesion might be to alternate the polarity of the electrical field every half hour to one hour, ensuring that the electric field was applied early on before excessive die-back of axons occurred.

"Final Thrusts Prepared in RES," Spinal Cord Society Newsletter, pp. 3-4 (June, 1987), states that the Center for Paralysis Research at Purdue University has developed an Oscillating Field Stimulator "which carefully alternates the directions and amounts of current flow to [sic] maximum growth from both directions to the point of completion" to overcome the difficulty of nerve fiber dieback.

R. Borgens, A. Blight, D. Murphy & L. Stewart, "Transected Dorsal Column Axons Within the Guinea Pig Spinal Cord Regenerate in the Presence of an Applied Electrical Field," Journal of Comparative Neurology, 250:168-180 (1986), discloses that a steady state DC electrical field stimulates axons to grow into the glial scar in guinea pigs having partially severed spinal cords.

R. Borgens, A. Blight and M. McGinnis, "Behavioral Recovery Induced by Applied Electric Fields After Spinal Cord Hemisection in Guinea Pig," Science, 238:366-369 (October 16, 1987), discloses that an applied steady state DC electrical field promotes axonal regeneration in spinal cords of adult guinea pigs. It also discloses that in 25 percent of the experimental animals to which the field was applied, functional recovery of the cutaneous trunci muscle reflex occurred where no such recovery occurred in the control animals.

M. Wallace, C. Tator and I. Piper, "Recovery of Spinal Cord Function Induced by Direct Current Stimulation of the Injured Rat Spinal Cord," Neurosurgery, Vol. 20, No. 6, Part 1 (1987), discloses that direct current stimulation of the spinal cords of rats who have undergone a clip compression injury enhances the inclined plane performance of such rats as compared to control rats. It also discloses that the prognosis for recovery of function after a major spinal cord injury is poor because of the low regenerative capacity of the mammalian spinal cord.

U.S. 4,774,967 discloses a method and apparatus for in vivo mammalian nerve regeneration of a damaged nerve using an electric current through the damaged nerve while the nerve ends are abutted against one another, sutured together or spaced apart from each other. It also discloses that it is well known that there are substantial differences between a mammalian nervous system and other nervous systems. Further, it discloses that in the central nervous system of mammals, unaided attempts at regeneration often are quickly aborted by the body. It also discusses that the implantation of embryonic cells should provide a suitable environment for promoting and supporting growth of the lesioned adult central of peripheral nervous system.

M. Politis and M. Zanakis, "Short Term Efficacy of Applied Electric Fields in the Repair of the Damaged Rodent Spinal Cord: Behavioral and Morphological Results," discloses that the application of a DC stimulus to the injured spinal cord of rats with the cathode oriented rostrally enhanced the performance of such on the inclined plane test in comparison with rats having the anode oriented rostrally or with rats in

which no electrical field was applied. This paper also discloses that the mammalian central nervous system normally lacks the capacity to regenerate and achieve some functional restitution after damage. Applicants do not believe that this paper is prior art to their application. The copy of this paper enclosed herewith is a copy of the manuscript of the paper which applicants received which applicants understand was accepted for publication in Neurosurgery on April 22, 1988. The abstract entitled "Partial Recovery from Spinal Cord Injury Following Application of D.C. Electric Fields in the Rat," by M. Zanakis and M. Politis, appears to be an abstract for a presentation of the results described in the Neurosurgery article. Similarly, M. Zanakis and M. Politis, "Short Term Behavioral and Histological Changes in the Damaged Rat Spinal Cord Following Application of D.C Electric Fields," appears to be a short article presenting the same results as those described in the Neurosurgery article. Applicants are unsure whether any of these three documents have been published at this time. Applicants, however, received these documents after they had conceived and reduced their invention to practice.

The abstract entitled "The Effect of Localized Oriented Electric Fields on Regenerative Changes in Double Hemisectioned Spinal Cords of Rats," by M. Khan, M. Politis and D. Munoz-Garcia, discloses that the application of a localized oriented electric field enhances functional improvement although no difference was noted between rats with the cathode implanted rostrally and those with the anode implanted rostrally. Applicants again are unsure whether this abstract was published although it is believed that it was distributed at the June 25-27, 1987, Canadian Congress of Neurological Sciences.

M. Berry, "Regeneration in the Central Nervous System," Recent Advances in Neuropathology, Ch. 4, (1st ed. 1979) (Editors: W. T. Smith and V. B. Cavanaugh), discusses a variety of different techniques that have been used in an attempt to promote spinal cord regeneration in mammals. These techniques are evaluated in the context of a discussion of the reasons why the spinal cord in mammals will not regenerate. On page 71 it is noted that a difference in the regenerative capability of the central nervous systems of foetal and neonatal mammals as compared to mature mammals has been observed.

J. Kiernan, "Hypotheses Concerned with Axonal Regeneration in the Mammalian Nervous System," Biol. Rev., 54:155-197 (1979), discusses various hypotheses in an attempt to explain the difference between the regenerative capability of the peripheral nervous system, which is known to regenerate, and that of the central nervous system, which, with few exceptions, does not. This article does disclose that the immature central nervous system of mammals, i.e., foetal and possibly neonatal, does have some regenerative capability. [Id. at 170] This article also discloses that the neruones of the central nervous system have been observed to grow into grafts of peripheral nervous system tissue.

R. Borgens and M. McGinnis, "Artificially Controlling Axonal Regeneration and Development by Applied Electric Fields," Ch. 4, Electric Fields in Vertebrate Repair (1989), was published after this application was filed and thus is not prior art to this application. However, in this book chapter, applicants discuss the history of the use of applied electric fields to influence the growth of neurons. This discussion

identifies what applicants believe is likely the most pertinent prior art of which they are aware and direct the examiner's attention thereto. Applicants believe that which is discussed above is the most pertinent prior art and thus have not submitted copies of all the documents referenced in their book chapter. Upon a request by the Examiner, applicants will submit copies of any of the documents identified in their book chapter if possible.

Respectfully submitted,

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